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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,540	05/10/2007	Morihiro Mitsuya	BY0042P	4472

210 7590 05/13/2008

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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
05/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,540	MITSUYA ET AL.	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 14-16* is/are pending in the application.

4a) Of the above claim(s) *6 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9,10 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04-23-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Abstract

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. As an aid to future researchers, a structural formula of the claimed compounds should be given

Complete revision of the content of the abstract is required on a separate sheet.

Lack of Unity

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-5, 7, 9, 10 and 14-16, drawn to compounds of Formulas (I) and (I-1) in which X is CH, classified in class 544, subclasses 238, 284, *inter alia*, pharmaceutical compositions thereof and methods of treatment therewith, classified in class 514, subclasses 252.02, 266.21, 266.22, 266.23, inter alia.

II. Claims 1-4, 6, 8-10 and 14-16, drawn to compounds of Formulas (I) and (I-2) in which X is N, classified in class 544, subclasses 238, 279, inter alia,

pharmaceutical compositions thereof and methods of treatment therewith, classified in class 514, subclasses 252.02, 264.11, inter alia.

Each group as set forth above lacks unity with each other group, i.e., there is no single general inventive concept. The unique special technical features in each group are the identities of the compounds in regard to the A ring. The technical relationship between the inventions does not involve at least one common or corresponding special technical feature. The expression "special technical feature" is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. In this case, a reference that could be used to reject the compounds, processes medicaments and uses of Group I could not be used to reject the compositions, processes medicaments and uses of Groups II-III.

The Group I invention has special technical features not common to Group II and would be expected to be useful other than as disclosed, e.g., as intermediates to anti-cancer agents (US 5580870).

Restriction for examination purposes as indicated is proper because the inventions listed in this action are lacking in unity and are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

During a telephone conversation with Mr. Richard Billups on Apr. 3, 2008 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-5, 7, 9, 10 and 14-16, drawn to compounds of Formulas (I) and (I-1) in which X is CH, and pharmaceutical compositions thereof and methods of treatment therewith. Applicant must affirm this election in replying to this Office action. Claims 1-5, 7, 9, 10 and 14-16 are under examination only to the extent that they are drawn to compounds of Formulas (I) and (I-1) in which X is CH, and pharmaceutical compositions thereof and methods of treatment therewith. Otherwise, claims 1-5, 7, 9, 10 and 14-16 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected subject matter. In addition, claims 6 and 8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected invention of Group II.

Applicant is advised that a complete reply to this requirement must include (i) election of an invention to be examined though the requirement is traversed (37 CFR 1.143) **and (ii) identification of claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the lack of unity requirement, election shall be treated as an election without traverse. Traversal must be presented at the time of election to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

If applicants traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions are obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

In The Specification

Applicants are advised that, in the structural formulae illustrated at page 51, the last illustrated structural formula and all following formulae through the end of page 97, a hydrogen is missing from the bridging amine. Correction is required.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro glucokinase (GK) activating action, does not reasonably provide enablement for a method of treating diabetes mellitus (claim 15) or for a method of treating or preventing obesity (claim 16) with a compound of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following reasons apply to this enablement rejection.

At present no known drug can successfully prevent or reverse the course of obesity. "Prevent" means *to keep from happening, preclude, to anticipate,* etc. (Webster's Comprehensive Dictionary, 1996). The specification fails to teach one skilled in the art how to identify the host and therapeutic regimen for administration of the instant compounds to achieve the desired preventive effect. No evidence of record enables a skilled artisan to identify hosts with the potential to develop obesity.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). See *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) about testing needed to support *in vivo* uses.

Applicants is invited to review the Revised Interim Utility and Written Description Guidelines, 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. This disclosure is insufficient to enable the method claims based only on the disclosed activity.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration to determine whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) claim breadth; (2) nature of the invention; (3) state of the prior art; (4) level of predictability in the art; (5) amount of direction provided by the inventor; (6) presence of working examples; and (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

See also *In re Goodman* 29 USPQ2d 2010, 2013 (CAFC 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement.

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover pharmaceutical methods using thousands compounds of Formulas (I) and (I-1) in which X is CH.

(b) Scope of the diseases covered. The diseases construed by the claims have been described above. The specification fails to identify results of treatment with the methods of this invention in a mammalian patient.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is physiological in nature. The specification describes that the present compounds evidence *in vitro* GK activating action, and from that extrapolate that these compounds will treat diabetes mellitus (claim 15) and treat or prevent obesity. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is considered an unpredictable factor. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. **State of the prior art:** The art indicates the need for undue experimentation. Regarding a connection between GK activators and obesity and diabetes type 2, Al-Hasani, et al., Viewpoint: Molecular Interventions, Oct. 2003, Vol. 3, No. 7, pp. 367-370, report an area for clinical future research:

> Central administration of a GK activator such as RO-28-1675 **could**, for example, suppress neuronal circuits in the hypothalamus and the brain stem, thereby regulating appetite and energy expenditure as a consequence of constantly activated glucose sensors in the brain despite the lack of caloric intake. **In case** these compounds can be transported across the blood brain barrier and bypass the central appetite regulatory systems, weight loss **might** be achieved and **future** development of drugs to fight obesity as well as diabetes type 2 **might** be possible.

The ability of an agent that exhibits GK activating action shown in the specification to treat all diseases-conditions construed by the claims remains open to further study and proof.

5. **Working Examples:** Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.

6. **Skill of those in the art:** Al-Hasani questions the ability of a single class of compounds to effectively treat all types of diseases and/or conditions construed by the claims; they confirm the need for additional research.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed herein, indicates the requirement for undue experimentation.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7, 9, 10 and 14-16 are rejected under 35 U.S.C. 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim subject matter which applicant regards as the invention. Claim 1 is confusing and ungrammatical in the definition of ring A, "said heteroaryl group may have one substituent(s), being the same or different, selected from ..." The definition of R1(4) is confusing in the recitation that "said R1 may have one to ...," because it is not clear where or how such additional groups are bonded and it is not clear is such groups may be bonded to any of the R1 group. Because there is more than one heteroaryl group (R1(1) and ring A), it is not possible to determine which heteroaryl group is intended. If there is only one substituent, the plural recitation is confusing and ungrammatical. In

the definition of "said hydrogen atom," the "oxy group" is an incomplete moiety. In the definition of the α-group, "heteroary" is a misspelling. It is not understood how a "hydrogen of hydroxyl group ... may be substituted ..." Hydrogen has only one available bonding valence and cannot be further substituted.

Rejections Under 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 5, 7, 10 and 14 are rejected under 35 USC 103(a) over Barker, et al., US 5580870, issued Dec. 2, 1996 describing 4-heterocyclic-substituted-quinoazolines (col. 2, line 33 – col. 3, line 43, *inter alia*) useful as anticancer agents. Note specifically 7-fluoro-N-1H-indol-5-yl-6-methoxy-4-quinazolinamine monohydro-chloride (Ex. 21), a position isomer of the presently claimed compounds.

One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds that are position isomers and/or alkyl homologs of the Barker compounds, because such structurally related compounds are expected to possess similar properties. It has been held that compounds that are structurally isomeric and/or homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results.

> An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.

In re Payne, 203 USPQ 245, 254 (CCPA 1979). See also *In re Papesch*, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 16 USPQ2d 1897 (Fed.Cir. 1991) (discussed in MPEP § 2144) for an extensive case law review pertaining to

obviousness based on close structural chemical compound similarity. See also MPEP § 2144.08, I[II.A.4(c). Compounds that are isomers (compounds that have the same functional groups arranged is a different positional format) and/or homologs (compounds differing by the successive addition of the same chemical group, e.g., by alkylene groups), as here, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 195 USPQ 426 (CCPA 1977). Barker establishes a prima facie case of obviousness for the presently claimed compounds. Absent the presentation of verifiable data establishing the unobviousness of the claimed compounds over Barker, this rejection is sound.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.

5/2/2008

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624